## REMARKS

Claims 3-4, 9-12, 14-15, and 17-18 are withdrawn.

Claim 1 has been amended to recite "[a] process for the production of L-ascorbic acid comprising:

(a) contacting an enzyme with a substrate which is selected from the group consisting of L-gulose, L-galactose, L-idose, and L-talose;

(b) converting the substrate directly into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions; and

(c) isolating L-ascorbic acid from the reaction mixture,

wherein said enzyme has (1) the amino acid sequence of SEQ ID NO: 2 or (2) an amino acid sequence with 90% sequence identity to SEQ ID NO: 2 and with the activity to produce L-ascorbic acid or (3) an amino acid sequence encoded by the DNA sequence of SEQ ID NO: 1 or (4) an amino acid sequence encoded by a DNA sequence that hybridizes under stringent hybridization and wash conditions to the DNA sequence of SEQ ID: 1 and having the activity to produce L-ascorbic acid." Support for this amendment is found in the specification at, for example, page 1, lines 1-2; page 2, lines 8-12; page 2, line 25 to page 3, line 9 and lines 27-29; in Examples 1-4 and Tables 1-4; and in original claims 1 and 5. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l) (8$^{th}$ ed. Rev. 5, August 2006, pp. 600-92 and 600-84).

Claim 2 has been amended to recite "[a] process for the production of L-ascorbic acid with an enzyme having (1) the amino acid sequence of SEQ ID NO: 2 or (2) an amino acid sequence with 90% sequence identity to SEQ ID NO: 2 and with the

activity to produce L-ascorbic acid or (3) an amino acid sequence encoded by the DNA sequence of SEQ ID NO: 1 or (4) an amino acid sequence encoded by a DNA sequence that hybridizes under stringent hybridization and wash conditions to the DNA sequence of SEQ ID: 1 and having the activity to produce L-ascorbic acid, whereby L-ascorbic acid is produced from a substrate which is selected from the group consisting of L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone, and L-talonic acid,

said process comprising the steps of:

(a) contacting the enzyme with the substrate,

(b) converting the substrate directly into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions; and

(c) isolating L-ascorbic acid from the reaction mixture." Support for this amendment is found in the specification at, for example, page 1, lines 1-2; page 2, lines 8-12; page 2, line 25 to page 3, line 9 and lines 27-29; in Examples 1-4 and Tables 1-4; and in original claims 2 and 5. *See id.*

Claim 8 has been amended to recite "[a] process for producing L-ascorbic acid comprising (a) contacting a substrate which is selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, and L-galactonic acid with an enzyme derivable from *G. oxydans* DSM 4025, (b) converting the substrate directly into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions and (c) isolating L-ascorbic acid from the reaction mixture; wherein the enzyme has the following physico-chemical properties ...." Support for this amendment is found in the specification at, for example, page 1,

lines 1-2; page 2, lines 8-12; page 2, line 25 to page 3, line 9 and lines 27-29; in Examples 1-4 and Tables 1-4; and in original claims 5 and 8. *See id.*

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

**Objection:**

Claims 1, 2, and 8 were objected to because of the phrase "catalytical activity." (Paper No. 20070430 at 2). The Examiner suggested "amending the phrase to recite 'catalytic activity.'" (*Id.*).

With a view towards furthering prosecution, and as suggested by the Examiner, claims 1, 2, and 8 have been amended to recite "catalytic activity." In view of the foregoing amendment, the objection of claims 1, 2, and 8 has been rendered moot. Accordingly, withdrawal of the objection is respectfully requested.

**Indefiniteness Rejection:**

Claims 1 and 6-7 were rejected under 35 USC § 112, second paragraph. (Paper No. 20070430 at 2).

For the reasons set forth below, the rejection has been rendered moot.

In making the rejection, the Examiner asserted that claim 1 (from which claims 6-7 depend) recites the phrase "'... having the activity to produce L-ascorbic acid,' [and] it is not clear to the examiner ***what are the substrates*** for a polypeptide sequence comprising an amino acid sequence having 90% sequence identity to SEQ ID NO: 2." (*Id.*) (emphasis added).

As is well settled, all that is required to comply with 35 USC §112, second paragraph, is that the metes and bounds of what is claimed be determinable with a

reasonable degree of precision and particularity. *Ex parte Wu*, 10 USPQ2d 2031, 2033 (BPAI 1989).

Here, claim 1(a) ***explicitly recites*** "contacting an enzyme with a substrate which is selected from the group consisting of L-gulose, L-galactose, L-idose, and L-talose." One skilled in the art would readily recognize the substrates recited in the claims. There is nothing vague or indefinite about any of the recited substrates. Nothing more is required under 35 USC §112, second paragraph.

In view of the foregoing, the rejection of claims 1 and 6-7 cannot stand. Accordingly, withdrawal of the rejection is respectfully requested.

**Enablement Rejection:**

Claims 1-2, 6-8, 13, and 16 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. (Paper No. 20070430 at 3).

In making the rejection, the Examiner asserted that "the specification does not reasonably provide enablement for a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 [ ] from any source including variants, mutants and recombinants and encoded by the polynucleotide of SEQ ID NO: 1 or an amino acid encoded by a polynucleotide that hybridizes to SEQ ID NO: 1 under stringent hybridization conditions and said polypeptide under any conditions ...." (*Id.*).

The Examiner acknowledged, however, that the specification is "enabling for the production of L-ascorbic acid comprising: contacting an enzyme having the amino acid sequence of SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1, said polypeptide expressed in a specific strain of *E. coli* JM 109 having the activity to produce L-ascorbic acid from substrates L-gulono-1,4-lactone/L-gulonic acid from L-gulose and from L-galactono-1,4-lactone/L-galactonic acid or conversion of substrate L-galactose to L-galactono-1,4-lactone/L-galactonic acid and L-ascorbic acid under suitable culture conditions ...." (*Id.*).

At bottom, the rejection recognizes that the claims are enabled for the specific enzyme recited, but strangely not for highly homologous enzymes, *i.e.*, those that are at least 90% identical and have the same function as the recited enzyme.

As is well settled, it is the Examiner's burden to demonstrate that a specification is not sufficiently enabling. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). To carry his/her burden, the Examiner must identify and clearly articulate the factual bases and supporting evidence that allegedly establish that undue experimentation would be required to carry out the claimed invention. *Id.* at 370.

The rejection, however, fails to identify or articulate any factual basis or supporting evidence to establish that undue experimentation is required to practice the invention. At best, the Examiner asserts that "[t]he specification is limited to teaching the use of an enzyme having the amino acid sequence of SEQ ID NO: 2 with the activity to produce L-ascorbic acid under specific defined process conditions ..., but provides no guidance with regard to the making of other variants, mutants and recombinants from any source or with regard to other uses ...." (Paper No. 20070430

at 5). This conclusory statement falls short for at least two reasons. First, it impermissibly shifts the burden to the Applicant absent a *prima facie* case by the Examiner. Second, the statement ignores unambiguous disclosure in the specification how to make and screen for highly homologous enzymes having the same function as the recited enzymes.

With respect to the first deficiency, we note that "[i]n order to make a rejection, ***the examiner has the initial burden*** to establish a reasonable basis to question the enablement provided for the claimed invention.... ***[T]he minimal requirement is for the examiner to give reasons*** for the uncertainty of the enablement. ***This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments***." MPEP § 2164.04 (8th ed. Rev. 5, August 2006, p. 2100-191) (emphasis added).

Thus, it is simply not enough to attempt shift the burden to the applicant by asserting that the specification does not contain evidence of enablement, as the Examiner does here. At bottom, the rejection is completely devoid of the factual basis or supporting evidence required to establish a *prima facie* case for lack of enablement.

We further note that independent claims 1, 2, and 8 have been amended to explicitly recite ***a direct one-step conversion of a substrate into L-ascorbic acid***. As amended, these claims recite, *inter alia*, "converting the substrate ***directly*** into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions." Thus, amended claims 1, 2, and 8 now ***clearly recite*** a process that, *inter alia*, is ***a direct conversion*** of a recited substrate into L-ascorbic acid via Enzyme B (or highly

homologous enzymes having the same function as Enzyme B) acting as a biocatalyst. For this reason alone, the rejection should be withdrawn.

As is well accepted, even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. MPEP § 2164.05 and *In re Wands*, 8 USPQ at 1404. In addition, "a patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01 (8th ed. Rev. 5, August 2006, p. 2100-187) *citing In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). *See also Ex parte Kubin*, 2007 WL 2070495, *8 (BPAI 2007) (stating in the context of molecular biology that "[t]he amount of experimentation to practice the full scope of the claimed invention ***might have been extensive, but it would have been routine***. The techniques necessary to do so were well known to those skilled in the art.") (emphasis added).

Here, the Applicants have developed a novel process for ***direct production*** of L-ascorbic acid using an enzyme, which previously had been known but for another purpose or catalytic reaction. This is a significant and unexpected advancement in the art. The currently amended claims define the process steps required for ***a direct one-step conversion of a substrate into L-ascorbic acid***, the process being catalyzed by an enzyme of the present invention. The specification gives several examples of enzymes encompassed by the claims, including functional equivalents, enzymes encoded by DNA which hybridize to the DNA of SEQ. ID NO:1,

and mutants generated by various listed methods. (*See*, *e.g.*, Specification at pages 4-5). Indeed, the specification exemplifies 34 different amino acid substitutions and different screening assays for identifying functionally equivalent mutants. (*See* Specification at page 4). Therefore, the specification clearly enables the skilled person to identify enzymes in order to perform the presently claimed process, particularly in view of the fact that the physico-chemical properties (such as pH-optimum, pH-stability, substrate specificity, and molecular weight) as well as the amino acid and nucleotide sequences are known.

For example, the specification discloses the physico-chemical properties of Enzyme B of *G. oxydans* DSM 4025 as having:

(a) molecular weight of about 60,000 Da on SDS-PAGE;

(b) substrate specificity for primary and secondary alcohols and aldehydes;

(c) pH-stability at pH of about 6 to about 9;

(d) pH-optimum at pH of about 8.0; and

(e) inhibited by $Cu^{2+}$, $Zn^{2+}$, $Mn^{2+}$, $Fe^{2}$, and $Fe^{3+}$.

(Specification at page 1, lines 22-28). The specification also incorporates by reference EP 0 832 974 A2, which discloses Enzyme B of *G. oxydans* DSM 4025. The specification also discloses the amino acid sequence and nucleotide sequence for Enzyme B represented by SEQ ID NO: 2 and SEQ ID NO: 1, respectively. (*Id.* at page 2, lines 1-5). In addition, the specification discloses that "functional equivalents of the enzyme can be made either by chemical peptide synthesis known in the art or by recombinant means on the basis of the DNA sequences as disclosed herein by

methods known in the state of the art. Amino acid exchanges in proteins and peptides which do not generally alter the activity of such molecules are known in the state of the art." (*Id.* at page 4, lines 1-8). And, as an example of a functional equivalent, the specification discloses that a "functional equivalent of the enzyme includes an amino acid sequence encoded by a DNA sequence of SEQ ID NO: 1 ... as well as the complementary strand, or those which include the sequences, DNA sequences which hybridize under standard conditions with such sequences or fragments thereof ...." (*Id.* at page 4, lines 9-21). The specification also discloses that "[a] mutant of the gene can be prepared by treating the gene or a microorganism carrying the gene with a mutagen such as ultraviolet irradiation, X-ray irradiation, γ-ray irradiation or contact with a nitrous acid, N-methyl-N'-nitro-N-nitrosoguanidine (NTG), or other suitable mutagens, or isolating a colony or clone occurring by spontaneous mutation or by standard methods of in vitro mutagenesis known in the art. Many of these methods have been described in various publications." (*Id.* at page 4, lines 31-36). The specification also specifically identifies the parameters for stringent hybridization and stringent wash conditions. (*Id.* at page 7, lines 10-27). The specification also contains four examples (Examples 1-4) that include assays for identifying enzymes that meet the recited elements of the claims.

In sum, the specification and knowledge in the art provide ample guidance to allow one of skill in the art to practice the currently claimed invention without undue experimentation. Accordingly, the rejection is factually insufficient to support a rejection for lack of enablement, and for this reason also, the rejection should be withdrawn.

We further note that the Examiner's theoretical calculations regarding the frequency of functional mutants, even if correct, which is not conceded, argues in favor of patentability. Indeed, the Federal Circuit has already considered – and soundly – rejected lack of enablement arguments solely on the number of routine screens that must be performed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1406-07 (Fed. Cir. 1988) (screening large numbers of hybridoma cell lines not found to be undue experimentation). Here, like *Wands*, a large number of mutants may need to be screened, but the screening procedures are routine and do not require undue experimentation. *See also Ex parte Kubin*, 2007 WL 2070495, *8 (BPAI 2007) (stating in the context of molecular biology that "[t]he amount of experimentation to practice the full scope of the claimed invention ***might have been extensive, but it would have been routine***. The techniques necessary to do so were well known to those skilled in the art.") (emphasis added).

For the reasons set forth above, the enablement rejection should be withdrawn.

**Rejections under 35 U.S.C. § 102(b):**

Claims 1, 2, 6-8, 13, and 16 were rejected under 35 USC § 102(b) as anticipated by Asakura *et al.*, EP 0 832 974 A2 ("Asakura"). (Paper No. 20070430 at 10-13).

For the reasons set forth below, the rejection, has been rendered moot.

Asakura discloses "a recombinant enzyme preparation having an alcohol and/or aldehyde dehydrogenase activity which comprises one or more enzymatic polypeptide(s) selected from the group consisting of polypeptides which are identified

by SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, and SEQ ID NO 8 ...." (Abstract). "[T]he AADHs provided ... can catalyze the oxidation of L-sorbose to 2KGA via L-sorbosone and/or the oxidation of D-sorbitol to L-sorbose. More particularly, the AADHs provided ... contain Enzyme A, Enzyme A', Enzyme A", and Enzyme B, which have the amino acid sequences shown in SEQ ID NO. 5, 6, 7, and 8, respectively." (Page 6, lines 5-10). Asakura further discloses at Table 1 the substrate specificities for Enzyme A, Enzyme A', Enzyme A", and Enzyme B using n-propanol, isopropanol, D-glucose, D-sorbitol, L-sorbosone, D-mannitol, L-sorbose, and D-fructose. (Page 7, lines 5-33).

In making the rejection, the Examiner asserted that Asakura "disclose[s] the purification, kinetic profiles and physico-chemical characterization of a polypeptide designated as Enzyme B from *G. oxydans* DSM 4025 that has 100% sequence homology to SEQ ID NO: 2 of the instant application with identical physico-chemical properties and substrate specificity for primary and secondary alcohols, optimal pH range, pH stability, thermal stability and effect of metals and inhibitors on the activity of said enzyme (Table: 1, 2 , 3 , 4 and 5 ...)." (Paper No. 20070430 at 11). The Examiner further asserted that "Table 10, page 23 discloses L-idose as a substrate for Enzyme B and the formation of L-idonic acid and the use of said enzyme in a process for the production of L-ascorbic acid and the intermediates of L-ascorbic acid (Abstract section). (*Id.* at 12). The Examiner then concluded that Asakura "anticipates" claims 1, 2, 5-8, 13, and 16. (*Id.*).

In response to Applicants' remarks submitted February 12, 2007, the Examiner further asserted that "neither the claims as written nor the specification

explicitly states that the said process for the production of L-ascorbic acid is a direct one step conversion of claimed substrates into L-ascorbic acid ...." (*Id.*).

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single ***prior art reference*** and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.,* 221 USPQ 481, 485 (Fed. Cir 1984). "Moreover, it is incumbent upon the Examiner to ***identify wherein each and every facet*** of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BPAI 1990). The Examiner is required to point to the disclosure in the reference "***by page and line***" upon which the claim allegedly reads. *Chiong v. Roland*, 17 USPQ2d 1541, 1543 (BPAI 1990).

As amended, independent claims 1, 2, and 8 now recite, *inter alia*, "converting the substrate ***directly*** into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions." Direct conversion is clearly described in the specification. For example, the specification discloses "(a) contacting the enzyme with the respective substrate and (b) isolating the respective product from the reaction mixture." Thus, the specification clearly conveys to one skilled in this art that <u>one</u> enzyme directly converts <u>the</u> substrate into <u>the</u> product. No other interpretation is reasonable. And, one skilled in the art would clearly recognize the currently amended claims as explicitly reciting a ***direct conversion*** of the identified substrates into L-

ascorbic acid via the recited enzyme acting as a biocatalyst, ***without any further steps needed or intermediates being formed***.

The specific use of the recited enzyme for a direct one step-conversion of the claimed substrates into L-ascorbic acid is ***not*** disclosed by Asakura. Asakura discloses a process for the conversion of several substrates (see Table 10) into products including, e.g., D-gluconic acid, L-sorbose, 2-KGA, D-fructose, L-idonic acid. None of the disclosed products is the currently claimed L-ascorbic acid. Further, as discussed, the currently claimed process does not require any chemical step or isolation of an intermediate, such as, for example, 2-KGA, in order to arrive to the final product, L-ascorbic acid. The claimed process utilizes one enzyme. Thus, Asakura ***fails*** to disclose or suggest the currently claimed process, *i.e.*, a ***direct conversion*** of the recited substrates into L-ascorbic acid, *e.g.*, L-idose to L-ascorbic acid as currently claimed. Accordingly, the rejection is insufficient as a matter of law and fact to support a conclusion of anticipation, and for this reason, the rejection should be withdrawn.

In view of the claim amendments, the rejection has been rendered moot and should be withdrawn.

Claims 2, 8, 13, and 16 were also rejected under 35 USC § 102(b) as anticipated by Sugisawa *et al.*, Isolation and Characterization of New Vitamin C Producing Enzyme (L-gulono-g-lactone dehydrogenase) of Bacterial Origin, Biosci. Biotech. Biochem., 1995, Vol. 59(2): 190-196 ("Sugisawa"). (Paper No. 20070430 at 13-14).

For the reasons set forth below, the rejection, has been rendered moot.

Sugisawa discloses that "*G. oxydans* DSM 4025 produced 8.57 and 13.9 mg of L-ascorbic acid per ml from 70.3 and 89.3 mg of L-gulono-γ-lactone per ml in the growing and resting cell systems, respectively." (Abstract). "The enzyme was isolated from the soluble fraction of the cells of *G. oxydans* DSM 4025 by DEAE-cellulose, Q-Sepharose, hydroxylapatite, and Sephacryl S-300 column chromatographies." (*Id.*). "[T]he enzyme consisted of three kinds of subunits of $M_w$ 61,000±1000, 32,500±1000, and 16,500±500 (Fig. 2B)." (Page 193).

In making the rejection, the Examiner asserted that Sugisawa "disclose[s] the purification, kinetic profiles and physico-chemical characterization of a polypeptide derived from *G.oxydans* DSM 4025 that produced L-ascorbic acid from L-gulono-γ-lactone said enzyme consisted of 3 subunits of molecular weight of about 61,000 +/- 1000, 32,500 +/- 1000 and 16,500 +/- 500 with identical physico-chemical properties and substrate specificity, optimal pH range, pH stability, thermal stability and effect of metal and inhibitors on the activity of said enzyme (Abstract section)." (Paper No. 20070430 at 13-14). The Examiner further asserted that "Tables: I, II, IV, V, VI and VII disclose production of L-ascorbic acid, substrate specificity, effects of temperature, pH and various metals on the activity of said enzyme." (*Id.* at 14). The Examiner further asserted that "[c]laims 2, 13 and 16 are included in the rejection although said claims recite specific SEQ ID NO: 2 and the activity of said polypeptides under specific pH and temperature, because examiner interprets these properties to be inherent in the isolated polypeptide." (*Id.*). The Examiner then concluded that Sugisawa "anticipates" claims 2, 8, 13, and 16. (*Id.*).

As stated above, anticipation requires "identity of invention." *Glaverbel Societe Anonyme,* 33 USPQ2d at 1498. Each and every element recited in a claim must be found in a single ***prior art reference*** and arranged as in the claim. *Marshall*, 198 USPQ at 346; *Lindemann Maschinenfabrik GMBH,* 221 USPQ at 485. "Moreover, it is incumbent upon the Examiner to ***identify wherein each and every facet*** of the claimed invention is disclosed in the applied reference." *Levy*, 17 USPQ2d at 1462. The Examiner is required to point to the disclosure in the reference "***by page and line***" upon which the claim allegedly reads. *Chiong*, 17 USPQ2d at 1543.

As amended, independent claims 1, 2, and 8 now recite, *inter alia*, "converting the substrate ***directly*** into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions." One skilled in the art would clearly recognize these claims as explicitly reciting a ***direct conversion*** of the identified substrates into L-ascorbic acid via the recited enzyme acting as a biocatalyst, ***without any further steps needed or intermediates being formed***.

The specific use of Enzyme B for a direct one step-conversion of the claimed substrates into L-ascorbic acid is also ***not*** disclosed by Sugisawa. ***Sugisawa does not even disclose the claimed enzyme***. As admitted by the Examiner, the enzyme disclosed in Sugisawa is approximately 110 kDa consisting of 3 subunits approximately 61,000 +/- 1000, 32,500 +/- 1000, and 16,500 +/- 500 kDa, respectively. (Paper No. 20070430 at 14). In contrast, the claimed enzyme, Enzyme B, consists of only 1 subunit of about 60 kDa. A further difference between the claimed enzyme and the enzyme disclosed in Sugisawa is the activity of the enzyme on the substrate L-galactono-1,4-lactone. Table VIII of Sugisawa discloses that the isolated enzyme has

no activity on the substrate L-galactono-1,4-lactone, whereas the claimed enzyme clearly displays activity on this substrate. (*See* Sugisawa at page 195, Table VIII vis-à-vis Example 4, Table 4 of the Specification). Accordingly, the rejection is insufficient as a matter of law and fact to support a conclusion of anticipation, and for this reason, the rejection should be withdrawn.

In view of the foregoing, the rejection has been rendered moot and should be withdrawn.

**Rejection under 35 U.S.C. § 103:**

Claims 1, 2, 6-8, 13, and 16 were rejected under 35 USC § 103 as being unpatentable over Asakura in view of Boudrant, J., *"Microbial Processes for Ascorbic Acid Biosynthesis: A Review,"* Enzyme Microb. Technol. v. 12, pp. 322-329 (1990) ("Boudrant") and Hancock, R. and Viola, R., *"Biotechnological Approaches for L-Ascorbic Acid Production,"* Trends in Biotechnology, v. 20, no. 7, pp. 299-305 (2002) ("Hancock"). (Paper No. 20070430 at 14; Paper No. 20060728 at 11).

The rejection respectfully is traversed. At the outset we note that all arguments made in this paper concerning the art, the other rejections, etc. are readopted and reasserted with respect to this rejection as if fully set forth here. Accordingly, the earlier explanation of why the anticipation rejection over Asakura fails applies with equal force to this obviousness rejection.

Asakura is summarized above.

Boudrant discloses that "L-Ascorbic acid is an important product currently made using the Reichstein process, which is mainly chemical. Recently, bacteria have been identified that are able to transform in a very efficient way glucose to 2,5-keto-D-

gluconic acid and this product to 2-keto-L-idonic acid, precursor of L-ascorbic acid. When the corresponding strains are used together, it is possible to get 2-keto-L-idonic acid directly from glucose. Moreover, new strains have been constructed by introducing a gene from a strain responsible for the second step into a strain responsible for the first step. By using one of the new strains, the transformation can be performed in a single step with only one strain." (Abstract).

Boudrant discloses that "[a]t present there are six bacterial fermentation processes for vitamin C production. However, all of these processes give as a direct precursor of L-ascorbic acid, 2-keto-L-gulonic acid, which is also called 2-keto-L-idonic acid." (Pages 322-323). "The different pathways, named after one of their main metabolic intermediates, are the following:

1. Sorbitol pathway;
2. L-idonic acid pathway;
3. L-gulonic acid pathway;
4. 2-keto-D-gluconic acid pathway;
5. 2-5-diketo-D-gluconic acid pathway;
6. 2-keto-L-gulonic acid pathway."

(Page 323).

Hancock discloses "the development of biotechnological alternatives for the synthesis of Reichstein intermediates by industrial microorganisms. The recent elucidation of the plant biosynthetic pathway represents new opportunities not only for the direct synthesis of $_{L}$-AA by fermentation but also for the production of human crop plants and animal fodder with enhanced nutritional value." (Abstract). Hancock states in its conclusion that "[t]he Reichstein process has come to the end of its reign," and "[r]ecent advances in our understanding of $_{L}$-AA biosynthesis in plants and $_{D}$-EAA

biosynthesis in yeast will pave the way for the development of novel methods for direct $_L$-AA production." (Page 304).

In making the rejection, the Examiner relied on Asakura, the primary reference, as "teach[ing] the purification, kinetic profiles and physico-chemical characterization of a polypeptide designated as Enzyme B from *G.oxydans* DSM 4025 that has 100% sequence homology to SEQ ID NO: 2 of the instant application with identical physicochemical properties and substrate specificity (as discussed in 102 (b)) rejection above)." (Paper No. 20060728 at 11).

The Examiner acknowledged, however, that Asakura "is silent regarding [] some of the substrates selected from the group L-gulose, L-galactose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-talono-1,4-lactone and L-talonic acid." (*Id.*).

To fill the acknowledged gap, the Examiner relied on Boudrant and Hancock for "teach[ing] the different processes and conditions for the production of L-ascorbic acid, such as The Reichstein process, bacterial fermentation processes and the different pathways, substrates and products such as L-sorbose, L-gulonic acid, L-idonic acid to 2-keto-L-gulonic acid or 2-keto-L-idonic acid utilized by bacteria and the enzymes produced by the bacteria in the production of L-ascorbic acid (entire document)." (*Id.* at 11-12).

The Examiner then concluded that "[c]ombining the teachings of the above references, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to develop a process for the production of L-ascorbic acid using the enzyme taught by Asakura et al., wherein they disclose the different

substrates and intermediate products made by Enzyme B from *G.oxydans* DSM 4025 including the substrate L-idose and intermediate product L-idonic acid and further suggest enzyme's use in L-ascorbic acid synthesis. One of ordinary skill in the art would have been motivated to make or use such an enzyme in the production of L-ascorbic acid and one of ordinary skill in the art would have had a reasonable expectation of success, since the references of Bourdant et al., and Hancock et al., (supra) teach the various pathways and a list of intermediates and substrates that can be employed for the production of L-ascorbic acid, further strengthening the motivation and reasonable expectation of success to use Enzyme B of *G.oxydans* DSM 4025 with the substrates disclosed in the present invention for the production of L-ascorbic acid." (*Id.* at 12).

In response to Applicants' remarks submitted February 12, 2007, the Examiner further asserted that "nowhere in any of the claims is it explicitly stated that the claimed process is a one-step process for the production of L-ascorbic acid ...." (Paper No. 20070430 at 15). Moreover, the Examiner asserted that the JM109 bacterial strain (disclosed in Examples 1-4 of the specification) "is interpreted to comprise many other enzymes that are involved in the conversion of other claimed substrates into intermediates, said intermediates are acted upon ... to form L-ascorbic acid." (*Id.*).

Initially, we note independent claims 1, 2, and 8 now recite, *inter alia*, "converting the substrate ***directly*** into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions." One skilled in the art would clearly recognize these claims as explicitly reciting a ***direct conversion*** of the identified substrates into L-

ascorbic acid via the recited enzyme acting as a biocatalyst, ***without any further steps needed or intermediates being formed***.

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *Glaug*, 62 USPQ2d at 1152. Moreover, in attempting to set forth a *prima facie* case for obviousness the Examiner is required to consider the claimed invention as a whole (*i.e.*, consider each and every limitation of the claimed invention). "In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983)." (MPEP § 2141.02, 8th ed., Rev. 2, May 2004, p. 2100-124 to 2100-125) (emphasis original).

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to

combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added). *See also* Examination Guidelines for Determining Obviousness, 72 Fed. Reg. 57526, 57528 (October 10, 2007) ("The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.").

The rejection, however, again, contains no such showing. Instead, the Examiner has decided to, again, pick and choose from the disclosure of Asakura, Boudrant, and Hancock. Here, even if Boudrant and Hancock were properly combinable with Asakura, which they are not, the proposed combination still would not disclose or suggest the currently claimed process. Boudrant discloses the biotransformation of D-glucose via several intermediates into 2-keto-L-gulonic acid (2-KGA) or 2-keto-L-idonic acid by the help of various bacteria. The final intermediates, *i.e.*, 2-keto-L-gulonic acid (2-KGA) or 2-keto-L-idonic acid, are then ***further processed via chemical transformation*** to L-ascorbic acid (*see, e.g.*, page 326, paragraph 4, left column, and Figure 2). Boudrant speculates that it would be useful to have a process with only one biotransformation step. In other words, a process wherein the last step, *i.e.*, conversion of 2-KGA into L-ascorbic acid, would also be performed via a microbial process. (*See* page 327, last paragraph, right column). Because this conversion includes both a reduction and an oxidoreduction, Boudrant suggests that ***at least two enzymes*** would be required to perform said conversion. (*Id.*). Following the disclosure of Boudrant and starting from L-idonic acid as one intermediate mentioned therein, one

would require at least 3 enzymes to reach L-ascorbic acid. (*See* Figure 2 in connection with page 327, last paragraph, right column). The currently claimed process, however, requires something completely different, *i.e.*, the production of L-ascorbic acid from the recited substrates using ***only one specific enzyme***. Thus, Boudrant does not fill the gap in Asakura.

Similarly, Hancock discloses a summary of the then currently known bacterial biotransformation processes starting from D-glucose. Also, just like Boudrant, Hancock discloses that the biological process ends with 2-KGA, which is then followed by chemical conversion to arrive at L-ascorbic acid. (See, e.g., page 300, Figure 2). Hancock further *speculates* on a bioconversion from D-glucose via 2-KGA to L-ascorbic acid. (*See* page 302, second paragraph, left column). However, there is no suggestion or disclosure of a bacterial process using the claimed substrates together with the specific recited enzymes as to ***directly arrive*** at L-ascorbic acid without an intermediate (such as 2-KGA). Thus, Hancock also does not fill the gap in Asakura. And, the combination of the both Hancock and Boudrant also does not fill the gap in Asakura.

Thus, Asakura either alone or in combination with Boudrant and/or Hancock neither discloses nor suggests the currently claimed process. For this reason alone, the rejection should be withdrawn.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based

upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

As amended, independent claims 1, 2, and 8 recite, *inter alia*, "converting the substrate ***directly*** into L-ascorbic acid by catalytic activity of the enzyme under suitable culture conditions." Asakura, Boudrant, and Hancock, either alone or in combination, fail to disclose the currently claimed process, *i.e.*, a ***direct conversion*** of the identified substrates into L-ascorbic acid via the recited enzyme acting as a biocatalyst, ***without any further steps needed or intermediates being formed*** (*e.g.*, L-ascorbic acid production from L-gulose or L-ascorbic acid from L-galactose). There is simply no suggestion or motivation in any of the cited documents of a direct one-step process as claimed, *i.e.*, using only one enzyme, Enzyme B. This direct conversion of the identified substrates into L-ascorbic acid via the claimed enzyme is disclosed in the specification at, for example, Examples 1-4 and Tables 1-4. These Examples and Tables compare a non-recombinant *E. coli* strain JM109 with a strain where Enzyme B was introduced. The non-recombinant *E. coli* strain JM109 consistently shows no vitamin C production, whereas the strain where Enzyme B was introduced shows vitamin C production of between 1.2 mg/l to 42.5 mg/l. This is clear evidence that Enzyme B is able to catalyze the direct conversion of the identified substrates into L-ascorbic acid. And this is ***not*** disclosed or suggested by any of the cited documents,

which describe completely different pathways, *e.g.*, from yeast[1] and plants[2]. *See Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). For this reason also, the rejection is deficient and should be withdrawn.

This is also evidence that notwithstanding the Examiner's sheer speculation that other JM109 enzymes may be involved in the currently claimed processes, all that is required is the recited enzyme and the recited substrates. The Examiner's speculation about "other enzymes" simply misses the mark.

We further note that the rejection is also devoid of any discussion of the dependent claims separate from the independent claims. Accordingly, the record is devoid of any evidence that the Examiner individually considered the dependent claims. It is axiomatic, however, that a dependent claim is not *per se* obvious based on alleged prior art that allegedly makes obvious the base claim. Accordingly, "[e]xaminers are reminded that a dependent claim is directed to a combination including everything recited in the base claim and what is recited in the dependent claim. ***It is this combination that must be compared with the prior art, exactly as if it were presented as one independent claim.***" MPEP § 608.01(n) (8th ed., Rev. 5, Aug.

[1] Boudrant discloses that yeast is capable of the conversion of L-gulonic acid into L-ascorbic acid via L-gluono-1,4-lactone.
[2] Hancock discloses the production of L-ascorbic acid from L-galactose via L-galactono-1,4-lactone in plants.

2006, pp. 600-91). This the Examiner has not done. Accordingly, the rejection is also both factually and legally deficient as to the dependent claims. For this additional reason, the rejection should be withdrawn as to the dependent claims.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the rejections, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on November 12, 2007.

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